

**A Study to evaluate the safety and effectiveness of the Left atrial
appendage closure therapy Using BSJ003W for patients with non-valvular
atrial fibrillation at increased risk of ThromboEmbolic in Japanese
medical environment**

SALUTE

CLINICAL INVESTIGATION PLAN

S6001

Sponsored By

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Investigational Sites	A list of study sites is provided in Appendix.
Clinical Trial Organization	Clinical trial organization is listed in an attachment (Investigational sites and investigators are included.)

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2. Protocol Synopsis

A study to confirm the safety and effectiveness of the BSJ003W in Japanese patients with non-valvular atrial fibrillation at increased risk of thromboembolism in Japanese clinical environment	
Study Objective(s)	To confirm the safety and effectiveness of the BSJ003W in Japanese patients with non-valvular atrial fibrillation at increased risk of thromboembolism in Japanese Clinical environment
Planned Indication(s) for Use	To reduce the risk of thromboembolism from the Left Atrial Appendage in patients with non-valvular atrial fibrillation who are at increased risk based on CHADS ₂ or CHA ₂ DS ₂ -VASc scores
Test Device	BSJ003W LAA Closure Technology; three-component system consisting of the <ul style="list-style-type: none"> • BSJ003W Closure Device; WATCHMAN(Gen 2.5) • BSJ003W Delivery System (Delivery Catheter and BSJ003W Closure Device) • BSJ003W Access System (Access Sheath and Dilator)
Control Device	None
Device Sizes	21mm, 24mm, 27mm, 30mm, 33mm
Study Design	This is a prospective, multi-center, single-arm study to confirm the safety and effectiveness of BSJ003W for Japanese subjects with non-valvular atrial fibrillation who are eligible for long-term anti-coagulation therapy to reduce the risk of stroke but who have a rationale to seek a non-pharmacologic alternative in Japanese clinical environment.
Planned Number of Subjects	1 Roll-in subject per site is required prior to enroll an analyzable subject at each site. One more Roll-in subject should be enrolled if necessary per Investigators' or a proctor's discretion. Number of analyzable patients: 40 patients. Maximum of 60 subjects (including 10-20 Roll-in subjects) will be enrolled in the study.
Planned Number of	Up to 10 investigational centers in Japan

A study to confirm the safety and effectiveness of the BSJ003W in Japanese patients with non-valvular atrial fibrillation at increased risk of thromboembolism in Japanese clinical environment	
Investigational Sites	
Primary Endpoints	<p>To assess safety and effectiveness of BSJ003W, the following three endpoints are established as Co-Primary Endpoints:</p> <ol style="list-style-type: none">1. The occurrence of one of the following events between the time of implant and within 7 days following the procedure or by hospital discharge, whichever is later: all-cause death, ischemic stroke, systemic embolism, or device- or procedure- related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair. Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm and nonsurgical treatments of access site complications are excluded from this endpoint.2. The occurrence of composite events* including stroke (all/ ischemic/ hemorrhagic), systemic embolism and CV death (including unexplained cause) . *All data collected up to the last patient's 6 months follow-up visit to be completed.3. The rate of effective LAA closure* at 45 days and 6 months. Change in the rate between the two time points will also be analyzed. *The effective LAA closure is defined as peri-device flow \leq 5mm demonstrated by TEE. TEE measurements will be assessed by independent Core Lab.

A study to confirm the safety and effectiveness of the BSJ003W in Japanese patients with non-valvular atrial fibrillation at increased risk of thromboembolism in Japanese clinical environment	
Secondary endpoints	<p>Safety endpoints:</p> <ul style="list-style-type: none"> The occurrence of major bleeding* at 0 – 45 days, 45 days – 6 months, 6 months – 24 months <p>*Major bleeding is defined as per BARC bleeding definition type 3 or 5</p> <ul style="list-style-type: none"> Frequency of the following bleeding events at 0 – 45 days, 45 days – 6 months and 6 months – 24 months: Clinically overt non-fatal bleeding* All bleeding events <p>*Clinically overt non-fatal bleeding is defined as per BARC bleeding definition type 2.</p> <p>Effectiveness endpoints:</p> <ul style="list-style-type: none"> The occurrence of composite events* for effectiveness; stroke (all/ ischemic/ hemorrhagic), systemic embolism and CV death (including unexplained cause) <p>*All data collected up to the last patient's 12 months and 24 months follow-up visits to be completed.</p> <ul style="list-style-type: none"> Effective LAA closure at 12-month and its time course until then. The occurrence of ischemic stroke or systemic embolism (excluding 7 days after implanting or day after hospital discharge whichever is the later) at 6 months, 12 months and 24 months.
Additional Endpoints	<p>Device performance:</p> <ul style="list-style-type: none"> Technical Success defined as successful delivery and release of BSJ003W into the LAA including successful recapture and retrieval if necessary. <p>Safety endpoints:</p> <ul style="list-style-type: none"> Occurrence of reportable adverse events Occurrence of all-cause mortality <p>Effectiveness endpoints:</p> <ul style="list-style-type: none"> Individual occurrence of all-cause death, ischemic stroke,

A study to confirm the safety and effectiveness of the BSJ003W in Japanese patients with non-valvular atrial fibrillation at increased risk of thromboembolism in Japanese clinical environment		
	<p>hemorrhagic stroke, systemic embolization, cardiovascular death (including unexplained cause) at 6-month, 12-month and 24-month.</p> <ul style="list-style-type: none"> Warfarin discontinuation rate at 45 days, 6-month and 12-month Severity of stroke assessed by NIH Stroke Score, Modified Rankin Scale Score, and Barthel Index <p>Other endpoint:</p> <ul style="list-style-type: none"> EQ-5D 	
Required Medication Therapy	Visit	Medication
	Implant through 45-day visit	ASA+ Warfarin
	45-day visit through 6-month visit	ASA+ Thienopyridine
	Following the 6-month visit	ASA
	<p>Warfarin therapy should be appropriately monitored and adjusted so as to achieve a therapeutic INR of 2.0- 3.0. For a subject who are 70 years old or older, a therapeutic INR of 2.0 – 2.6 is recommended considering the high risk of major bleeding. Subjects should remain on warfarin until the 45-day TEE evaluation has shown adequate seal of the LAA. If the LAA is not adequately sealed, the subjects should be on warfarin and Aspirin therapy.</p>	
Follow-up Schedule	<p>Study procedures and follow-up visits will occur as follows:</p> <ul style="list-style-type: none"> Informed consent Screening BSJ003W Implant 45-day Follow-up (45 ± 15 days) 6-Month Follow-up (182 ± 30 days) 12-Month Follow-up (365 ± 30 days) 18-Month Follow-up (547 ± 60 days) 24-Month Follow-up (730 ± 60 days) 	
Study Duration	<p>The duration of the study is expected to last approximately 3 years. The duration of individual subject participation is expected to last</p>	

A study to confirm the safety and effectiveness of the BSJ003W in Japanese patients with non-valvular atrial fibrillation at increased risk of thromboembolism in Japanese clinical environment	
	approximately 2 years.
Key Inclusion Criteria	<ol style="list-style-type: none"> 1. The subject is Japanese, over 20 years old and provides written informed consent to participate in the trial 2. The subject has documented paroxysmal, persistent or permanent non-valvular atrial fibrillation 3. The subject has a calculated CHA₂DS₂-VASc score of 2 or greater and is recommended for long-term oral anti-coagulation therapy 4. The subject is deemed by their physicians to be suitable for anticoagulant therapy and have an appropriate rationale to seek a non-pharmacologic alternative to warfarin 5. The subject is eligible to come off warfarin therapy if the LAA is sealed (i.e. the subject has no other conditions that would require warfarin therapy).
Key Exclusion Criteria	<ol style="list-style-type: none"> 1. The subject has a prior stroke (ischemic or hemorrhagic) or TIA within the 90days prior to consent 2. The subject has had a MI either non-ST elevation or ST elevation MI within 90days prior to consent with or without intervention 3. The subject had or is planning to have any cardiac (e.g. cardioversion, coronary angiogram, percutaneous coronary intervention, cardiac ablation, etc.) or non-cardiac invasive or surgical procedure (e.g. cataract surgery, endoscopy, etc.) within 30 days prior or 45 days after the BSJ003W implant 4. The subject has a history of atrial septal repair or has an ASD/PFO device 5. The subject has an implanted mechanical valve prosthesis in any position 6. The subject currently NYHA class IV CHF 7. The subject is contraindicated to aspirin 8. The subject is contraindicated or seriously allergic to thienopyridine 9. The subject is of childbearing potential and is, or plans to become pregnant during the time of the study (method of assessment upon study physician's discretion) 10. The subject is not able and willing to return for required follow-up

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	<p>visits and examinations</p> <ol style="list-style-type: none"> Subjects who are currently enrolled in another investigational study (of which primary endpoint follow-up have not been completed yet). The subject has other reason not to be eligible for this study per investigators' discretion.
ECHO Exclusion Criteria	<ol style="list-style-type: none"> The subject has LVEF < 30%. The subject has intracardiac thrombus visualized by TEE within 2 days prior to implant. The subject has an existing pericardial effusion with a circumferential echo-free space > 5mm, and/or the patient has signs/symptoms of acute or chronic pericarditis, and/or there is evidence (clinically or echocardiographically) of tamponade physiology. The subject has a high- risk patent foramen ovale (PFO) with an atrial septal aneurysm excursion > 15mm or length \geq 15mm. The subject has a high-risk PFO with a large shunt defined as early, within 3 beats, and/or substantial passage of bubbles. The subject has significant mitral valve stenosis (i.e., MV <1.5 cm²). The subject has complex atheroma with mobile plaque of the descending aorta and/or aortic arch. The subject has a cardiac tumor.
Multiple Interventions During Index Procedure	<p>No concomitant procedures are to be performed at the time of the BSJ003W implant procedure. This includes, but is not limited to, cardiac ablation procedures, transcatheter valve procedures, cardioversions, pacemaker or ICD generator change, etc.</p>
Statistical Methods	
Statistical consideration and Sample size justification	<p>The primary safety endpoint event rate observed in the PREVAIL study was 2.2%. Based on the PREVAIL data only, the exact 95% upper confidence bound for this rate is 4.4%. An additional margin of 5.6% is added to this upper confidence bound to create a performance target of 10.0. In order to maintain \geq95% probability that the observed estimate from this study is lower than the performance target of 10.0%, 40 subjects are required.</p> <p>The expected primary effectiveness endpoint rate is 99.3%. Based on this expected rate, and the number of subjects in the PREVAIL study with 6-month TEEs, the corresponding exact 95% lower confidence bound is 97.3%. An additional margin of 3.3% is subtracted from this lower</p>

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	confidence bound to create a performance target of 94.0%. Accounting for 10% attrition to 6-month TEE follow-up, 40 subjects are required to maintain $\geq 95\%$ probability that the observed estimate from this study is higher than the performance target of 94.0%.
Statistical Test Method	<p>Similarities of this study results will be evaluated with foreign pivotal study results.</p> <p>Roll-in patients' data will be evaluated separately from the data of those patients enrolled after the Roll-in patients and will not be included in the endpoint analysis.</p>

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4. Introduction

4.1. Background

Atrial fibrillation (AF) is one of the most common abnormal rhythm disturbances and affects approximately 5.5 million people worldwide, including 10% of people older than 75 ¹years. Prevalence of AF in Japan in 2005 was 0.56% (0.72 million people) and it is expected to increase over 1% in 2050 with aging population. The most debilitating consequence of non-valvular atrial fibrillation (NVAf) is thrombus formation from stagnant blood flow leading to thromboembolism and stroke. In cardiogenic stroke, an abrupt closure of cerebral artery from floating thrombus could cause severe ischemia with large infarction. Patient condition could be more serious than those who have Lacunar or atheroma stroke and patient care could be an serious issue. The rate of ischemic stroke attributed to NVAf is estimated to average 5% per year, which is 2-7 times that of those without AF².

Treatment with warfarin therapy for the prevention of thromboembolism originating in the left atrial appendage by assessing its risk through CHADS₂ and CHA₂DS₂-Vasc has been well documented in Japanese/US/EU guidelines of AF treatment ³⁻⁵. While warfarin has remained the optimum treatment, there are numerous challenges with the drug. It is a big concern for patients and their care takers not to be able to completely avoid fatal bleeding and other bleeding events with ill prognosis due to its pharmacological effect. HAS-BLED score, therefore, is proposed to predict such bleeding during anticoagulation therapy which has been used in the Japanese/US/EU guidelines and proper management is recommended.

Warfarin has relatively narrow therapeutic range, and frequent need for monitoring and dosage adjustments, good daily patient compliance, tolerance and dietary and metabolic interactions are concerned. Bleeding is especially concerned in Japan and only 50% patients with CHADS₂ of more than 2 and it is reported that even if treated with Warfarin, low dose tend to be administered².

Currently available alternatives to warfarin are the direct oral anticoagulants (DOACs), which include dabigatran, rivaroxaban, apixaban, and edoxaban. Unlike warfarin, DOACs can be administered without the need for monitoring, have fewer food and drug interactions. However, bleeding risk is not completely avoidable even with DOAC, risk of bleeding is increased with age, weight and renal function¹⁰⁻¹², and patient tolerance and compliance as with Warfarin are still concerned. Non-pharmacological therapy alternative to oral anticoagulation therapy, therefore, is necessary. Symptomatic AF patients with intolerance to pharmacological therapy are treated with catheter ablation. However, in addition to complications associated with high frequency ablation/cryotherapy and it is difficult to apply them to elderly or CHF patients, and their indication is limited since results is not always optimal for persistent or permanent AF. Furthermore, long term effect, stroke prevention and improvement of prognosis have not been clearly identified.

The sponsor has developed the BSJ003W Left Atrial Appendage Closure (LAAC) Device, a permanent implantable device to seal off the left atrial appendage, the location where more than 90% of thrombi in atrium originate in NVAf patients. Safety and effectiveness of BSJ003W in NVAf patients who need reduction of thromboembolic events were evaluated in foreign clinical trials with Warfarin as a control. As a result, non-inferiority to Warfarin in

reduction of thromboembolism was confirmed, discontinuation of Warfarin reduced the risk of hemorrhagic stroke and bleeding events and cardiovascular death (including unexplained cause) was found to be reduced more than Warfarin¹⁴⁻¹⁸. In comparison with Warfarin, BSJ003W was able to reduce cardiovascular death by 56% whereas DOAC reduced 12%, and therefore, BSJ003W may also be more beneficial to those NVAF patients who are eligible for the device as far as DOAC is concerned. BSJ003W can provide an alternative to NVAF patients who require thromboembolic protection and especially with history of bleeding and cerebral infarction, high risk of bleeding, noncompliance with anticoagulation, continuous administration of anticoagulation is considered not appropriate due to their medical history, renal function and/or liver function and high risk of trauma from occupational conditions or life style,.

5. Device Description

5.1. Medical Equipment Description

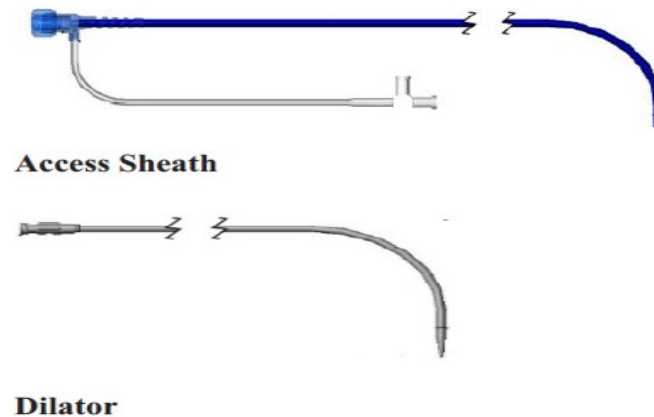
The BSJ003W LAA Closure Technology featuring BSJ003W consists of the BSJ003W Access System (which consists of the Access Sheath and Dilator **Figure 1**) and the BSJ003W Delivery System (which consists of the Delivery Catheter and the pre-loaded BSJ003W Closure Device, **Figure 2**). The BSJ003W Access System and BSJ003W Delivery System permit device placement in the LAA via femoral venous access and crossing the inter-atrial septum into the left atrium. The placement procedure can be done under local or general anesthesia in a catheterization laboratory.

5.1.1. BSJ003W Access System (Access Sheath and Dilator)

The 14F (12F Inner Diameter) transseptal Access Sheath is utilized to gain access to the LAA and serves as a conduit for the BSJ003W Delivery System. The distal end of the Access Sheath is available in three different curve styles to assist with placement of the sheath into the LAA. These curve styles allow for coaxial placement of the sheath into the LAA. The distal tip of the Access Sheath contains a marker band for in situ visualization as well as sizing marker bands used to gauge if the Access Sheath is positioned at the appropriate depth in the LAA based on the Closure Device size selected.

The Access Sheath and Dilator are utilized to gain access to the LAA after initial transseptal access into the left atrium has been established. Once the Access Sheath is positioned into the left atrium and the Dilator has been removed, the Access Sheath then serves as a conduit for the Delivery System. The Delivery System is introduced into the Access Sheath and the components snap together to act as one during device implantation.

Figure 1: BSJ003W Access System (Access Sheath/Dilator)



5.1.2. BSJ003W Delivery System and with Pre-loaded LAAC Device

The BSJ003W Closure Device is comprised of a self-expanding nitinol frame structure with fixation anchors around the Closure Device perimeter and a permeable polyester fabric that covers the atrial facing surface of the Closure Device (**Figure 2**). The Closure Device is constrained within the Delivery Catheter until deployment in the LAA.

The BSJ003W Closure (Gen 2.5) Device is available in 5 sizes from 21 to 33 mm. Closure Device selection is determined by LAA measurements using fluoroscopy (fluoro) and transesophageal echocardiography (TEE) (Table 5-1). The BSJ003W Closure Device is designed to be permanently implanted at or slightly distal to the ostium (opening) of the LAA to trap potential emboli before they exit the LAA.

Figure 2: BSJ003W Closure Device

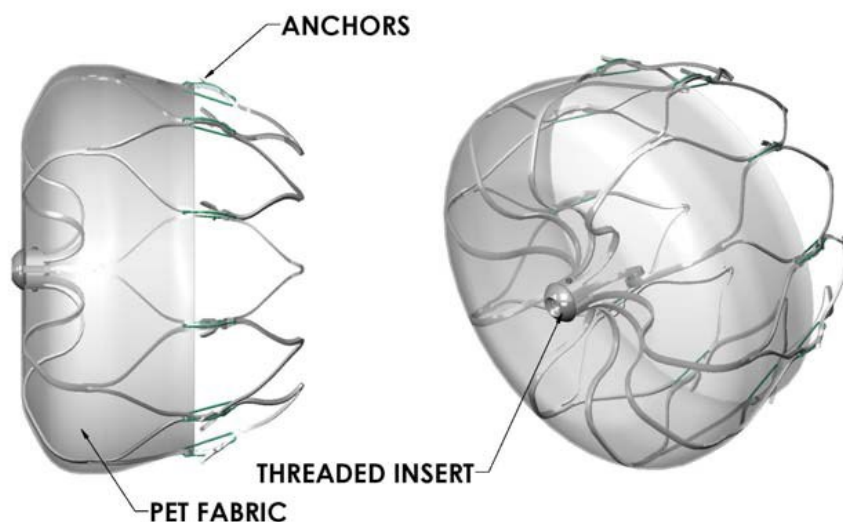


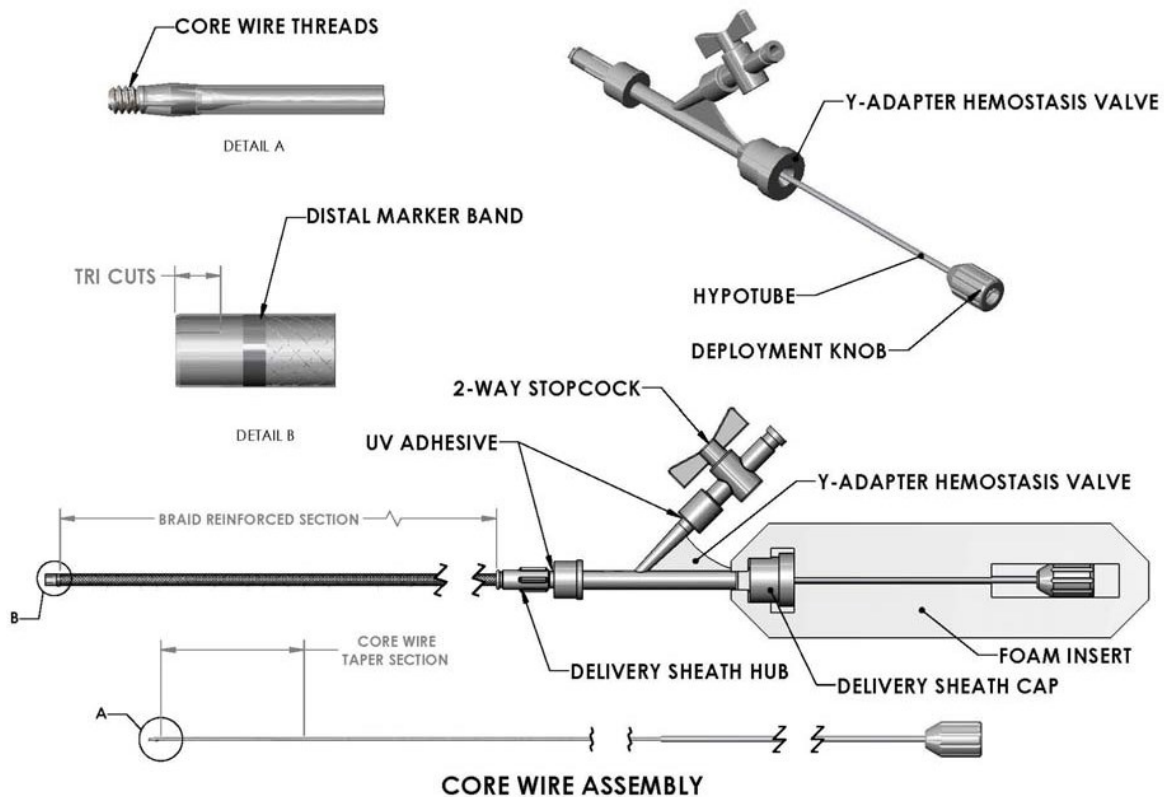
Table 5- 1 Device size and applicable LAA size

BSJ003W Device size	Maximum LAA ostium	Diameter at maximally crimped(20%)	Diameter at minimally crimped(8%)
21 mm	17-19 mm	16.8 mm	19.3 mm
24 mm	20-22 mm	19.2 mm	22.1 mm
27 mm	23-25 mm	21.6 mm	24.8 mm
30 mm	26-28 mm	24.0 mm	27.6 mm
33 mm	29-31 mm	26.4 mm	30.4 mm

The Delivery Catheter for BSJ003W consists of an inner core wire with a reinforced braided jacket that is connected to the deployment knob at the proximal end and a screw thread assembly at the distal end. The outer sheath has an overall profile of 12F.

The BSJ003W Closure Device is pre-loaded into a Delivery Catheter and is deployed by loosening the valve on the Delivery System and retracting the outer sheath. The BSJ003W Closure Device can be partially recaptured and redeployed if the device is too distal. If the Closure Device is deployed too proximal, it can be fully recaptured. The Closure Device is released by rotating the device deployment knob counter clockwise.

Figure 1 BSJ003W delivery system (delivery catheter and closure device)



5.2. *Indications for Use*

The BSJ003W Closure Device is indicated for left atrial appendage (LAA) closure therapy to reduce the risk of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Contraindications

Do not use the BSJ003W Closure Device if:

1. Intracardiac thrombus is visualized by TEE echocardiographic imaging.
2. An atrial septal defect repair or closure device or a patent foramen ovale repair or closure device is present.
3. The LAA anatomy will not accommodate a Closure Device (refer to the BSJ003W Closure Device Selection guide in the BSJ003W DFU).
4. The patient has a known hypersensitivity to any portion of the device material or the individual components (see Device Description in the BSJ003W DFU) such that use of the BSJ003W Closure Device is contraindicated.
5. Any of the customary contraindications for other percutaneous catheterization procedure (e.g. patient size too small for TEE probe or required catheters) or conditions (e.g., active infection, bleeding disorder) is present.
6. There are contraindications to the use of warfarin, aspirin, or thienopyridine

5.3. *Device Labeling*

The study Manual of Operations includes the Instructions for Use (IFU) for the BSJ003W LAA Closure Technology. The study devices are labeled which will include the following information. Packaging will include peelable, self-adhesive labels for each unit shipped.

- CAUTION: Clinical trial use only
- Study device ID
- Lot number
- Expiration (use by) date (labeled as month/year, device not to be used after the last day of the indicated month)
- Storage condition (if applicable)
- Sponsor name and address

6. Study Objectives

To confirm the safety and effectiveness of BSJ003W in Japanese patients with non-valvular atrial fibrillation at increased risk of thromboembolism in Japanese Clinical environment

7. Study Endpoints

7.1. Primary Endpoint

1. The occurrence of one of the following events between the time of implant and within 7 days following the procedure or by hospital discharge, whichever is later:
all-cause death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair.
Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm and nonsurgical treatments of access site complications are excluded from this endpoint.
2. The occurrence of composite events* including stroke (all/ ischemic/ hemorrhagic), systemic embolism and CV death (including unexplained cause) .
*All data collected by the last patient's 6 months follow-up visit to be completed.

3. The rate of effective LAA closure* at 45 days and 6 months. Change in the rate between the two time points will also be analyzed.
*The effective LAA closure is defined as peri-device flow \leq 5mm demonstrated by TEE. TEE measurements will be assessed by independent Core Lab.

7.2. Secondary Safety Endpoint

- The occurrence of major bleeding* at 0 – 45 days, 45 days – 6 months, 6 months – 24 months

*Major bleeding is defined as per BARC bleeding definition type 3 or 5

- Frequency of the following bleeding events at 0 – 45 days, 45 days – 6 months and 6 months – 24 months:

Clinically overt non-fatal bleeding*

All bleeding events*Clinically overt non-fatal bleeding is defined as per BARC bleeding definition type 2.

7.3. Secondary Effectiveness Endpoint

- The occurrence of composite events* including stroke (all/ ischemic/ hemorrhagic), systemic embolism and CV death (including unexplained cause)

*All data collected up to last patient's 12 months and 24 months follow-up visits to be completed.

- Effective LAA closure at 12-month and its time course until then.
- The occurrence of ischemic stroke or systemic embolism (excluding 7 days after implanting or day after hospital discharge whichever is the later) at 6 months, 12 months and 24 months.

7.4. *Additional analysis*

Device performance:

- Technical Success defined as successful delivery and release of BSJ003W into the LAA including successful recapture and retrieval if necessary.

Safety endpoints:

- Occurrence of reportable adverse events
- Occurrence of all-cause mortality

Effectiveness endpoints:

- Individual occurrence of all-cause death, ischemic stroke, hemorrhagic stroke, systemic embolization, cardiovascular death (including unexplained cause) at 6-month, 12-month and 24-month.
- Warfarin discontinuation rate at 45 days, 6-month and 12-month
- Severity of stroke assessed by NIH stroke score, Modified Rankin scale and Barthel Index

Other endpoint:

- EQ-5D

8. Study Design

This is a prospective, multi-center, single-arm study.

8.1. *Scale and Duration*

This study will be conducted at up to 10 centers and enroll maximum of 60 patients in Japan. Of the potential 60 subjects, 10-20 subjects will be Roll-in and 40 will be enrolled as analyzable subjects. Sites are required to enroll at least one Roll-in subject prior to enrollment of analyzable subjects. Two Roll-in subjects are allowed to be enrolled by the decision of proctor or investigator if needed. The use of Roll-in subjects will allow physicians to gain experience with the BSJ003W implant procedure prior to beginning enrollment of analyzable subjects.

Once screening is completed and BSJ003W is implanted, a subject will be followed at 45 days, 6 months, 12 months, 18 months and 24 months after the study procedure.

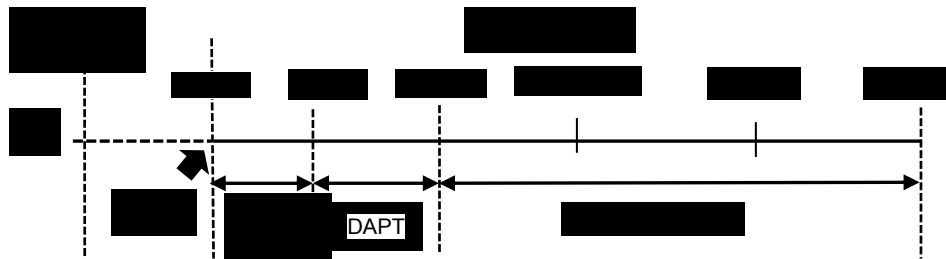


Figure 8.1-1: Study Design

8.2. Treatment Assignment

The study is designed to enroll subjects that meet all inclusion and no exclusion criteria.

8.2.1. Treatment

Refer to Section 5.0 for study device information and available sizes.

8.3. Justification for the Study Design

Safety and Effectiveness of BSJ003W in NVAf patients who need thromboembolic event prevention have been confirmed through results of foreign pivotal clinical studies using Warfarin therapy as their controls, i.e. non-inferior to Warfarin in prevention of thromboembolic events and superiority in prevention of hemorrhagic stroke and bleeding events by Warfarin discontinuation, and furthermore reduction of cardiovascular events (including unexplained death) more than Warfarin. (Refer to Section 5.0)

Objective of this study is to confirm safety and effectiveness of BSJ003W in Japanese medical environment when it's implanted in Japanese NVAf patients and confirm similarity of the study results to those from foreign pivotal clinical studies, and therefore, prospective single arm design was considered appropriate.

To evaluate safety, collect peri-procedural adverse events related to the procedure, and to evaluate expected effectiveness of BSJ003W action, composite endpoints of thromboembolic events and LAA closure rate will be confirmed.

Not only in PREVAIL study but also in other studies associated with anti-coagulation therapy, rate of thromboembolic events have been observed for two years, and so long term follow-up of safety and effectiveness in this study will be also evaluated for two years after BSJ003W implantation in the study procedure.

9. Subject Selection

9.1. Study Population and Eligibility

Any subject, who meets all the inclusion criteria, does not meet any of the exclusion criteria, and who provides written informed consent may be enrolled in the study. The subjects selected for participation will be from the investigators' general subject population. The investigator has the responsibility for screening all potential subjects and selecting those who meet study inclusion criteria and do not meet any of the exclusion criteria as described in sections 9.2 and 9.3. There are additional Echo exclusion criteria (section 9.4) that must be met.

9.2. Inclusion Criteria

Subjects who meet all of the following inclusion criteria (see Table 9.2-1) may be given consideration for inclusion in this clinical investigation.

Table 9.2-1: Inclusion Criteria

Clinical Inclusion Criteria	<ol style="list-style-type: none">1. The subject is Japanese, over 20 years old and provides written informed consent to participate in the trial2. The subject has documented paroxysmal, persistent or permanent non-valvular atrial fibrillation3. The subject has a calculated CHA₂DS₂-VASc score of 2 or greater and is recommended for long-term oral anti-coagulation therapy4. The subject is deemed by their physicians to be suitable for anticoagulant therapy and have an appropriate rationale to seek a non-pharmacologic alternative to warfarin5. The subject is eligible to come off warfarin therapy if the LAA is sealed (i.e. the subject has no other conditions that would require warfarin therapy).
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9.3. Exclusion Criteria

Subjects who meet any one of the following criteria (Table 9.3-1) will be excluded from this clinical study.

Table 9.3-1: Exclusion Criteria

Clinical Exclusion Criteria	<ol style="list-style-type: none">1. The subject has a prior stroke (ischemic or hemorrhagic) or TIA within the 90days prior to consent2. The subject has had a MI either non-ST elevation or ST elevation MI within 90days prior to consent with or without intervention3. The subject had or is planning to have any cardiac (e.g. cardioversion, coronary angiogram, percutaneous coronary intervention, cardiac ablation, etc.) or non-cardiac invasive or surgical procedure (e.g. cataract surgery, endoscopy, etc.) within 30 days prior or 45 days after the BSJ003W implant4. The subject has a history of atrial septal repair or has an ASD/PFO device5. The subject has an implanted mechanical valve prosthesis in any position6. The subject currently NYHA class IV CHF7. The subject is contraindicated to aspirin8. The subject is contraindicated or seriously allergic to thienopyridine9. The subject is of childbearing potential and is, or plans to become pregnant during the time of the study (method of assessment upon study physician's discretion)10. The subject is not able and willing to return for required follow-up visits and examinations11. Subjects who are currently enrolled in another investigational study (of which primary endpoint follow-up have not been completed yet).12. The subject has other reason not to be eligible for this study per investigators' discretion.
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9.4. *Echo Exclusion Criteria*

After informed consent and prior to or at the onset of procedure a TTE/TEE is performed. These additional exclusion criteria must be evaluated for each subject. If any of the Echo exclusion criteria are met, then the subject will be withdrawn from the study and will be classified as “INTENT” subject.

Table 9.4-1: Echo Exclusion Criteria

Echo Exclusion Criteria	<ol style="list-style-type: none">1. The subject has LVEF < 30%.2. The subject has intracardiac thrombus visualized by TEE and determined by the echocardiographer within 2 days prior to implant.3. The subject has an existing pericardial effusion with a circumferential echo-free space > 5mm, and/or the patient has signs/symptoms of acute or chronic pericarditis, and/or there is evidence (clinically or echocardiographically) of tamponade physiology4. The subject has a high- risk patent foramen ovale (PFO) with an atrial septal aneurysm excursion > 15mm or length \geq 15mm.5. The subject has a high-risk PFO with a large shunt defined as early, within 3 beats and/or substantial passage of bubbles.6. The subject has significant mitral valve stenosis (i.e., MV <1.5 cm²).7. The subject has complex atheroma with mobile plaque of the descending aorta and/or aortic arch.8. The subject has a cardiac tumor
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10. Subject Accountability

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. Until informed consent is signed by a patient, any study required tests and procedures must not be done.

10.1. *Point of Enrollment*

One Roll-in subject will be enrolled before analyzable subject will be enrolled at each site. If necessary per discretion of investigators and/or proctor, one more Roll-in subject can be enrolled at the site.

Subjects who meet the eligibility criteria, who have signed and dated the Informed Consent Form and a vascular access is inserted in the body are considered enrolled in the study. Each site should start enrolling analyzable subjects once enrollment of Roll-in subject is completed at each site. Enroll subjects once eligibility criteria are confirmed.

10.2. *Withdrawal*

If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to investigational device safety or performance, the

investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

10.3. Subject Status and Classification

10.3.1. Screen Failure

A subject who signs informed consent, but does not meet clinical eligibility criteria or does not undergo a vascular access inserted into the body in order to implant the device is considered a screen failure. **Screen failure subjects do not count towards the enrollment ceiling and will not be used for the primary analysis.** Additionally, these subjects will be included in a sensitivity analysis. The original signed Informed Consent must be maintained in the site and the following forms must be completed:

- Informed Consent Information, Screening Information, Inclusion Criteria, Exclusion Criteria, Echo Exclusion Criteria, Demographics

10.3.2. Attempt

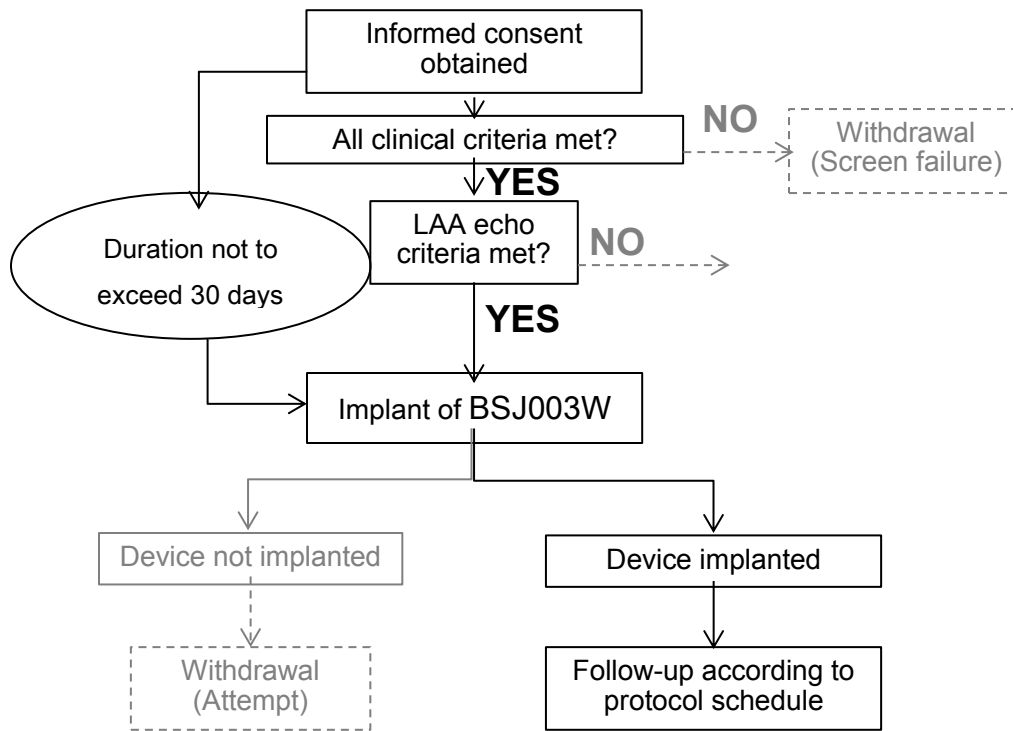
A subject who signs informed consent, meets all eligibility criteria (per Section 9.2, 9.3, and 9.4 of this Protocol) and has had a vascular access inserted into the body in order to implant the device, but eventually does not receive a BSJ003W Closure Device will be classified as "Attempt." Attempt subjects will be followed for 45 days from the time of the implant attempt and adverse events will be collected up to the point of subject withdrawal. Attempt subjects count towards the enrolment ceiling and will be used for analyses of the endpoints. The original signed Informed Consent must be maintained in the site and the applicable case report forms until 45 days visit must be completed

The date at which the "End of Study" form has been completed will be considered as the point of subject withdrawal.

10.3.3. Implant

A subject who is successfully implanted with the BSJ003W Closure Device will be classified as an "Implant." These subjects are followed in accordance with the follow-up schedule and included in all study analyses. All applicable case report forms per the protocol must be completed. The original signed Informed Consent and any relevant documentation must be maintained in the site.

Figure 2: Subject Status and Data Collection Flow Chart



10.4. Enrollment Controls

Subject enrollment into the BSJ003W Japan Study will be discontinued upon enrollment of 40 non-roll-in subjects with the BSJ003W Closure Device. The single site ceiling is up to 8 subjects. Beyond the limit, sponsor and site will communicate to enroll more subjects. Investigational sites will be notified when the enrollment goal is close to being reached and once enrollment is complete.

11. Study Methods

11.1. Data Collection

Table 11- 1 documents the information that will be requested at each visit.

For all IMPLANT subjects (successfully received the BSJ003W Closure Device) all visits are required, as defined in Table 11-1. For subjects classified as ATTEMPT, all visits up to and including the 45 day visit are required. The TEE is not required for these subjects.

Table 11-1: Data Collection Schedule

Procedure/Assessment	Screening	Implant	Follow-up Visits				
			45-Day (± 15 Days) Visit ^c	6-Month (180 days ± 15 Days) Visit	12 months (365 days ± 30 Days) Visit	18 months (540 days ± 60 Days) Visit	24 Month (730 days ± 60 Days) Visit
Informed consent form, including informed consent signature date	X						
Demographics	X						
Physical assessment	X		X	X	X	X	X
Medical history	X						
Transthoracic echocardiogram (TTE) ^a	X						
Transesophageal echocardiogram (TEE)	X ^b	X	X ^c	X	X		
Brain Imaging (MRI/CT)	As required ^d		As required ^d	As required ^d	As required ^d	As required ^d	As required ^d
Anticoagulant and antiplatelet medications	X		X	X	X	X	X
Modified Rankin Scale	X		X	X	X	X	X
NIH Stroke Scale	X		X	X	X	X	X
Barthel Index	X		X	X	X	X	X
Device and implant details		X					
Adverse event/ Device Deficiency monitoring		X ^g	X	X	X	X	X
eGFR and proteinuria	X						
EQ-5D	X			X	X	X	X

^aAn LVEF value obtained from a TTE performed within 90 days prior to consent may be used. If a significant cardiac event occurs after the TTE which causes a change in cardiac status [i.e., major CHF decompensation] the baseline TTE must be repeated prior to enrollment

^b Must be performed within 2 days prior to the study procedure or can be done at the study procedure but before implant of BSJ003W

^c For Attempt, no TEE is required

^d Obtain MRI/CT required if subject had prior stroke or TIA. A MRI or CT performed within in 90 days prior to consent may be used.

^eFor Attempt subjects the visit can be performed in office. For subjects classified as implant an office visit is required.

^g Adverse event/ Device deficiency monitoring is started from the time when subjects enter a catheterization suite or an operating room for BSJ003W procedure.

11.2. Informed Consent

In order to determine eligibility of a subject, the investigator needs to implement the consent process and verify and document the subject meets the inclusion/exclusion criteria. Informed consent is required from all subjects prior to the subject's participation in the study. The subject should be given ample time to consider participation and ask questions if necessary. An IRB-approved informed consent form must be signed and personally dated by the subject. The original, signed document is to be kept with the subject's file and a copy must be provided to the subject. The informed consent process must be documented by the person obtaining consent and the documentation must be placed in the site.

11.3. Screening Visit

Subjects selected for participation in this study should be from the investigator's general non-valvular atrial fibrillation population. Each investigator is responsible for screening all non-valvular atrial fibrillation subjects and selecting those who are appropriate for inclusion.

Subjects who meet the eligibility criteria as per 9.2, 9.3 and 9.4, and have signed and dated the Informed Consent Form are considered enrolled. The implant visit must occur within 30 days of consent.

The following will be assessed at the Baseline visit and documented on the Baseline case report forms for enrolled subjects:

- Demographics and medical history
- Physical assessment including vital signs (Height, Body weight, Blood Pressure and Heart rate)
- Current medication regimen for the use of antiplatelet and anticoagulation
- Modified Rankin Scale (MRS), NIH Stroke Scale (NIHSS) and Barthel Index (BI)
- Subjects with prior history of ischemic stroke, hemorrhagic stroke or TIA are required to have a Baseline MRI or CT obtained (up to 90 days prior to consent if no prior measurement is available)
- Transesophageal echocardiogram (TEE) prior to implant
- Transthoracic Echocardiogram (TTE) (up to 90 days prior to consent or if no prior measurement is available)
- eGFR (serum creatinine up to 6 months before consent or at enrollment if no prior measurement is available)
- Proteinuria (dipstick protein-dichotomized as urine dipstick protein none/trace vs. 1+ or higher)

- EQ-5D

11.4. LAA Imaging

After informed consent, all subjects will undergo an enrollment TEE and TTE.

All study required TEEs will be performed by protocol trained individuals and in accordance with the Imaging Manual. Copies of the TEE's will be sent to the Echo Core Lab per the Imaging Manual. Copies of all protocol required TEE imaging will be saved to disk media and available to the sponsor upon request. Certain information from TEEs conducted during the course of the study will be captured on the study case report forms. The site and subject identification number should be clearly identified on the media provided.

Certain information from TTEs conducted during the course of the study will be captured on the study case report forms.

1. Transthoracic Echocardiogram (TTE)

The enrollment TTE will be done to evaluate LVEF to confirm subject eligibility. An LVEF value obtained from a TTE performed within 90 days prior to consent may be used. If a significant cardiac event occurs after the TTE which causes a change in cardiac status [i.e., major Congestive Heart Failure (CHF) decompensation] the baseline TTE must be repeated prior to enrollment.

2. Transesophageal Echocardiogram (TEE)

All protocol required TEEs will be performed by protocol trained individuals and in accordance with the Imaging Manual. The Enrollment TEE will determine that all inclusion and exclusion criteria are met and must occur within 2 days prior to the implant. It may also occur on the same day as implant. The implant TEE will allow the investigator to obtain proper measurements of the LAA to correctly size the device, confirm device release criteria are met prior to device release, and confirm adverse events have not occurred during the implant procedure (i.e., pericardial effusion).

The 45-day, 6-month and 12-month TEEs are conducted to assess flow through and around the BSJ003W Closure Device and to verify there is no thrombus on the surface of the device. Adequate LAA seal is defined as little or no visible residual blood flow around the margins of the BSJ003W Closure Device in either a retrograde or antegrade fashion, with jet size \leq 5mm.

a. Stroke or Systemic Embolism TEE

In the event that a subject experiences a stroke or SE during the course of the study, supporting TEE documentation will be requested by the sponsor in an attempt to search for causes of stroke or embolic event. It is strongly encouraged to help better ascertain the mechanism of all strokes and SE. An optimal TEE evaluation includes, where feasible based on subject status and technical considerations, evaluation of:

- i. LA thrombus – size, location, mobility, etc.
- ii. BSJ003W Closure Device seal or presence (and measurement) of peri-device flow
- iii. BSJ003W Closure Device thrombus or pannus – size, location, mobility, etc.
- iv. Agitated saline contrast injection to evaluate presence of residual right to left shunt at the atrial level (persistence of PFO or residual puncture hole from transseptal catheterization for device placement)
- v. Presence, location and grade of ascending and arch aortic atheroma
- vi. Presence of worsening left ventricular dysfunction, “new” regional wall motion abnormality or presence of LV thrombus (LVEF data may be supplemented/substituted by TTE where appropriate, in addition to TEE parameters above)

b. Device Thrombus TEE

The most accurate determination of whether thrombus has formed on the surface of the BSJ003W Closure Device is through TEE evaluation. In the case of thrombus on the atrial facing side of the device, anticoagulation therapy should be initiated for approximately 12 weeks, or a longer period of time per hospital standard of care, for treatment of thrombus. After the course of anticoagulation therapy, a repeat TEE evaluation should be performed to confirm the thrombus has resolved. Cessation of anticoagulation after this timepoint is at the discretion of the investigator.

11.5. *Implant Procedure*

The implant visit must occur within 30 days of consent. The implant procedure should be performed using standard of care methods established by the investigational center (e.g. sterile technique, personnel requirements, etc.). Implantation of the BSJ003W Closure Device should only be performed with support of a proctor and a Field Clinical Specialist and by physicians trained in percutaneous and trans-septal procedures who have completed the BSJ003W physician training program. Refer to the BSJ003W Directions for Use (DFU) for detailed instructions regarding the implantation and use of the BSJ003W Closure Device.

Information collected during the implant procedure includes the following:

- BSJ003W Closure Device usage information
- Access System(s) usage information
- Device Release Criteria
- Device Deficiencies

- Adverse events experienced since previous visit

11.6. Study Medication Regimen (for subjects classified as Implant)

Protocol-required concomitant medications must be reported in the eCRF from the time of the enrollment visit through the 2 year follow-up. Information pertaining to the use of oral anticoagulants, thienopyridine and aspirin, including dose changes, medication interruptions, and medication cessation, must be documented. (See **Figure 3**).

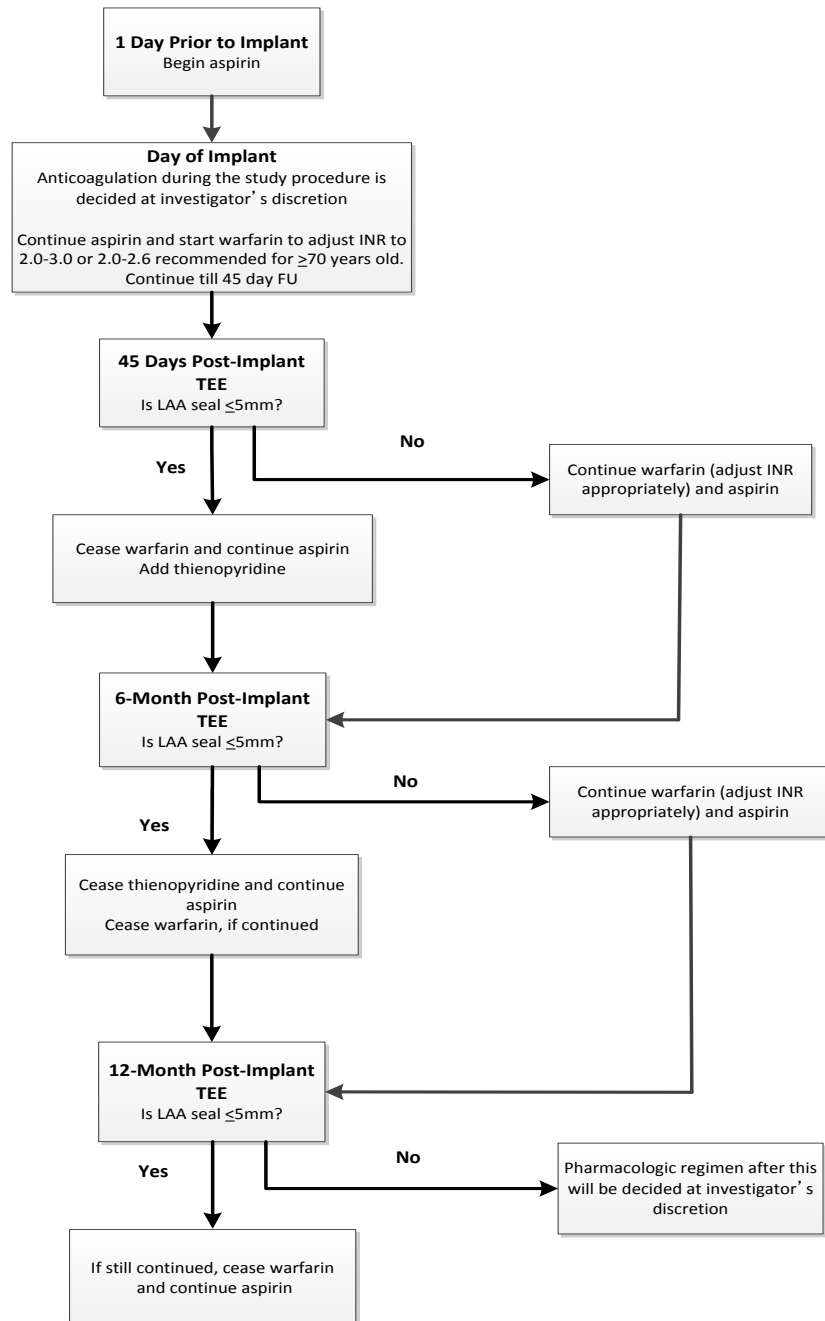


Figure 3: BSI003W Closure Device Implant Pharmacologic Regimen

▪ **Implant through 45-Day TEE**

Implanted subjects should be on adjusted dose warfarin therapy through at least the 45-day follow-up TEE. While on warfarin therapy, subjects should also be prescribed aspirin. Warfarin therapy should be appropriately adjusted so as to achieve a therapeutic INR of 2.0 – 3.0, monitored per standard of care. For a subject who are 70 years old or older, a therapeutic INR of 2.0 – 2.6 is recommended considering the high risk of major bleeding.

▪ **45-Day Visit**

A TEE will be conducted at the 45-day visit to assess position and the seal around the perimeter of the BSJ003W Closure Device within the LAA ostium. Adequate LAA seal is defined as little or no visible residual blood flow around the margins of the BSJ003W Closure Device in either a retrograde or antegrade fashion, with jet size $\leq 5\text{mm}$.

If the 45-day TEE shows adequate seal of the LAA with a jet around the device $\leq 5\text{mm}$:

- Warfarin therapy should be discontinued,
- Aspirin should be continued indefinitely, and
- Thienopyridine should be initiated, taken for 6-months post-implant, and then discontinued.

If the 45-day TEE shows inadequate seal of residual LAA blood flow with a jet size $> 5\text{mm}$ around the margins of device,

- The subject should remain on warfarin and aspirin therapy.
- Thienopyridine should not be initiated.

▪ **6-Month Visit**

A TEE will be conducted at the 6-Month visit. If the 45-day or 6-Month TEE shows adequate seal of the LAA:

- Warfarin therapy should be discontinued (If continuously prescribed after 45 days)
- Thienopyridine should be discontinued
- Aspirin should be continued indefinitely

If the 6-month TEE shows inadequate seal of residual LAA blood flow with a jet size $> 5\text{mm}$ around the margins of device,

- The subject should remain on warfarin and aspirin therapy.
- Thienopyridine should not be initiated.

▪ **12-Month Visit**

If the 45-day, 6-Month or 12-Month TEE shows adequate seal of the LAA:

- Aspirin should be continued indefinitely

If the 12-Month TEE shows inadequate seal of the LAA, anticoagulation and antiplatelet therapy after the 12-Month is at the discretion of the investigator.

Caution:

1. Use of direct oral anticoagulants (DOACs) in this study is not recommended since this has not been studied in subjects with a BSJ003W Device. If anticoagulation is required for any reason beyond what is specified in the protocol, ensure medication labeling is followed, specifically labeling related to the abrupt discontinuation of DOACs in subjects with non-valvular atrial fibrillation without adequate continuous anticoagulation.
2. No antiplatelet drug other than Aspirin was administered for long term in a clinical study, and therefore, no other antiplatelet drug but Aspirin is recommended in this study after 6 months post-implant. If administration of any antiplatelet drug like thienopyridine is required other than Aspirin, ensure medication labeling is followed.

11.7. *Stroke Assessments*

The Modified Rankin Scale (MRS) score and the Barthel Index score will be routinely collected at screening and follow-up visits for all subjects and at 90 (+/- 10) days following a stroke or TIA event. This scale assesses the severity of stroke disability and functional dependence of subjects. This test will be collected at baseline and all office follow-up visits. The assessment must be performed by either a neurologist or personnel who have completed a certification for the MRS.

The NIH Stroke Scale (NIHSS) is an assessment tool which quantifies stroke related neurological deficit. This assessment must be conducted in person to provide valuable information on stroke severity. This test will be performed at baseline and all office follow-up visits and if possible, following stroke. It must be conducted by a neurologist or personnel who have a current certification to conduct the NIHSS.

11.8. *QoL Assessments: EQ-5D*

The EQ-5D will be collected at baseline, at 6 months, 12 months, 18 months and 24 months office follow-up visits.

11.9. Follow-up Procedures at 45 days

11.9.1. For Subjects classified as Implants

Subjects successfully implanted with the BSJ003W Closure Device, “IMPLANT”, will complete an office visit 45-days post-implant with a TEE evaluation. Information collected during the 45-day visit includes the following:

TEE (as described in Section 11.5)
MRS, NIHSS and BI
Current medication regimen for the use of antiplatelet and anticoagulation medications (as described in Section 11.7)
Physical assessment including vital signs (Body weight, Blood Pressure and Heart rate)
Device-, procedure- and/or study-related adverse events, including device deficiencies experienced since previous visit
Stroke, SE and/or Thrombus TEE, if needed
Brain MRI or CT required if subject suffers stroke or TIA
Adverse events including device deficiencies experienced since previous visit

11.9.2. For Subjects classified as Attempts

Subjects who were NOT successfully implanted with the BSJ003W Closure Device will complete an office visit 45-days post procedure. Information collected during the 45-day visit for “ATTEMPT” subjects includes the following:

Adverse events including device deficiencies experienced since previous visit
TEE is not required for these subjects

11.10. Office Visit Follow-up (6-month and 12-month)

Information collected during the 6months and 12 months visit includes the following:

TEE
MRS, NIHSS and BI
Current medication regimen for the use of antiplatelet and anticoagulation medications (as described in Section 11.7)
Physical assessment including vital signs (Body weight, Blood Pressure and Heart rate)
Adverse events including device deficiencies experienced since previous visit
Stroke, SE and/or Thrombus TEE, if needed
Brain MRI or CT required if subject suffers stroke or TIA
EQ-5D

11.11. Office visit Follow-Up (18-month and 24-month)

“IMPLANT” subjects will complete an office visit 18 months and 24 months post implant.
Information collected during this visit includes:

MRS, NIHSS and BI
Current medication regimen for the use of antiplatelet and anticoagulation medications (as described in Section 11.6)
Physical assessment including vital signs (Body weight, Blood Pressure and Heart rate)
Adverse events including device deficiencies experienced since previous visit
Stroke, SE and/or Thrombus TEE, if needed
Brain MRI or CT required if subject suffers stroke or TIA
EQ-5D

11.12. Study Exit

Once a study subject has exited the study, their participation in the study has ended. Appropriate eCRFs are completed indicating the status of the subject (i.e., end of study form). The table below provides information on the appropriate eCRF's to complete.

Type of Study Exit	Date to Use	Form(s) to complete
Subject withdrawal	Date of subject withdrawal	End of Study form Adverse Event (resolve/close any AE's)
Subject Lost to Follow-up	Date subject was last seen in office	End of study Adverse Event (resolve/close any AE's)
Subject Death	Date of Death	Adverse Event (only one) with fatal outcome, resolve/close other AE's End of Study Form
Complete all protocol visits	Date of last study visit	End of Study Form Adverse Event (resolve/close any AE's)

11.13. Source Documents

Original source documents should be maintained, when available. Where copies of the original source document as well as printouts of original electronic source documents are retained, it is required that the copies be signed and dated by a member of the investigation site team with a statement that it is a true reproduction of the original source document.

Table 11.13-1: Source Documentation Requirements

Requirement	Disposition
Signed Informed Consent, patient charts including nursing records and catheterization record, lab results, study device accountability record, photographic negatives, radiographs and other hospital records, kept at the investigational sites, laboratories and medico-technical departments involved in the study.	Kept at investigational sites
Data if directly documented in the eCRF; e.g. relationship of AE to study device(s), index procedure and anticipatedness assessment of ADEs, will be considered source data for the study.	In the eCRF

12. Statistical Considerations

To discuss similarity of outcomes of this study and the foreign pivotal studies, working hypothesis was developed.

Data collected from Roll-in patients will not be included in the following endpoint analysis and will be analyzed separately from those data collected from patients enrolled after completion of the Roll-in.

12.1. Primary Safety Endpoints

Primary safety endpoint is the occurrence of one of the following events between the time of implant and within 7 days following the procedure or by hospital discharge, whichever is later:

all-cause death, ischemic stroke, systemic embolism, or device- or procedure- related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair.

Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm and nonsurgical treatments of access site complications are excluded from this endpoint.

Similarities of this study results will be evaluated with foreign pivotal study results.

12.1.1. Statistical Hypotheses

Not applicable.

12.1.2. Sample Size

The primary safety endpoint event rate observed in the PREVAIL study was 2.2% and an additional margin was added to create a performance target of less than 10.0%. Considering that 1-2 events may occur by chance, equal or more than 40 subjects will allow at least 3 events or more to occur and with $\geq 95\%$ probability, observed estimate from this study is lower than the performance target .

12.1.3. Statistical Methods

Each event will be evaluated individually and occurrence rate and 95% CI will be calculated.

12.2. *Primary Efficacy Endpoints*

Primary efficacy endpoints are the occurrence of composite events including stroke (all/ ischemic/ hemorrhagic), systemic embolism and CV death (including unexplained cause) and the rate of effective LAA closure at 45 days, 6 months and change in rate between the two time points.

12.2.1. Hypotheses

Not applicable.

12.2.2. Sample Size

A performance target of an effective LAA closure rate of this study, 94.0%, was created by considering an additional margin with 99.3% of the effective LAA closure rate observed in PROTECT AF and PREVAIL studies. Accounting for 10% attrition to 6-month TEE follow-up, 40 subjects are required to maintain $\geq 95\%$ probability that the observed estimate from this study is higher than the performance target of 94.0%. This will allow up to 2 patients whose LAA may not be effectively closed for any reasons at 6 months.

Meantime, sample size of 40 patients were established taken into consideration that 10% of pivotal study sample size was reasonable from standpoint of the study feasibility and similarity comparison of outcomes of this study and the pivotal studies.

12.2.3. Statistical Methods

The occurrence of composite events including stroke (all/ ischemic/ hemorrhagic), systemic embolism and CV death (including unexplained cause) as well as effective LAA closure rate will be calculated and similarities of this study results will be evaluated with foreign pivotal study results. All data collected up to the last patient's 6 month follow-up completion will be used for the analysis.

12.3. General Statistical Methods

12.3.1. Analysis Sets

Roll-in patients' data will be evaluated separately from the data of those patients enrolled after the Roll-in patients.

Intension-to-Treat(ITT) subjects are included in primary analysis for primary safety and efficacy endpoints as well as secondary endpoints and other endpoints. In addition, Implant subjects alone will be evaluated as needed as reference.

ITT: A subject who signs informed consent and regardless of the study device implanted or not, being enrolled into the study. IMPLANT and ATTEMPT subjects are included in ITT.

12.3.2. Control of Systematic Error/Bias

Selection of subjects for enrollment will be made from the Investigator's usual subject load. All subjects meeting the eligibility criteria and having signed the ICF will be eligible for enrollment in the study. To control for the potential bias that could be introduced via sponsor classification of adverse events, a Clinical Events Committee (CEC) will adjudicate important endpoints and relevant adverse events.

12.3.3. Number of Subjects per Investigative Site

To avoid any center effect and bias, one center will not be authorized to enroll more than 20% of the 40 subjects (n = 8) per this protocol. Further enrollment will require advance agreement from sponsor.

12.3.4. Data Analyses

Baseline and other results will be analyzed descriptively with continuous variables (mean, standard deviation, number of patients, minimum, maximum, etc) and discrete values (frequency table and percentage).

12.3.5. Other Endpoints/Measurements

Descriptive statistics will be used for other endpoints.

12.3.6. Interim Analyses

Interim analysis is not planned.

Initial analysis is planned at the last patient's 6 month follow-up completion and the second analysis at 12 month follow-up completion. Final analysis is planned once all follow-ups (24month follow-up) required by the study are completed.

12.3.7. Subgroup Analyses

Sub-group analysis will be completed, such as analysis by discontinue Warfarin, etc.

12.3.8. Justification of Pooling

Not applicable.

12.3.9. Multivariable Analyses

Univariate and multivariate analyses will be performed to assess predictors for Primary safety endpoint, primary efficacy endpoint and secondary endpoint. Details of the analysis will be included in Statistical Analysis Plan.

12.3.10. Other Analyses

Descriptive analysis will be used for other analysis.

12.3.11. Changes to Planned Analyses

Any changes to the planned statistical analyses will be documented in an amended Statistical Analysis Plan approved prior to the change. Changes from the planned statistical methods after completion of the statistical analysis will be documented in the clinical study report along with a reason for the deviation.

13. Data Management

13.1. Data Collection, Processing, and Review

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor or its representative. The associated RAVE software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

13.2. Data Retention

The investigator, head of medical institution and founder of the IRB will maintain all essential trial documents and source documents, in original format, that support the data

collected on study subjects in compliance with GCP guidelines. The documents must be retained until the date of the marketing application approval or until 3 years have elapsed since the formal discontinuation or completion of the clinical investigation of the device, whichever is longer.

These documents will be retained for a longer period of time by agreement with sponsor. If for any reason the Investigator and Site withdraw responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility. The Investigator and Site will take measures to ensure that these essential documents are not accidentally damaged or destroyed. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

The Sponsor must maintain necessary essential documents for 5 years from the date of the marketing application approval or until 3 years have elapsed since the formal discontinuation of the clinical investigation of the device, whichever is longer. If Re-Evaluation is applicable and requires more than 5 years to complete, the sponsor must maintain the essential documents until its completion.

13.3. *Core Laboratories*

An independent core laboratory will be utilized to review TEE imaging collected at protocol required time points during the study. All interpretations of TEE imaging for purposes of subject care will be conducted by each site's investigator and/or echocardiographer. The Core Lab will not be utilized as a means of reference for subject management decisions.

Imaging will be collected by each study site according to the Imaging Protocol and submitted to the Core Lab for review. The Core Lab will provide Boston Scientific with summary of results for reporting purposes and associated study endpoint analyses.

14. Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate IRB approval of the revised protocol must be obtained prior to implementation.

15. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using eCRF. Sites may also be required to report deviations to the IRB, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

16. Device/Equipment Accountability

The investigational devices shall be securely maintained, controlled, and used only in this clinical study. Vender will be used to track subjects and device allocations during the study.

The sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices from BSC or designated facility to the investigation sites until return or disposal.

Records shall be kept by the vender to document the physical location and conditions of storage of all investigational devices.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include the following

- Date of receipt
- Identification of each investigational device (batch number or unique code)
- Expiry date, as applicable
- Date or dates of use
- Subject identification
- Date on which the investigational device was returned/explanted from subject, if applicable
- Date of return (and number) of unused, expired, or malfunctioning investigational devices/equipment, if applicable.

Current sponsor processes will be used to track subjects and investigational device during the study. Upon completion of enrollment into the study, or as directed by the sponsor, all unused investigational devices must be returned to the sponsor.

17. Compliance

17.1. Statement of Compliance

This study will be conducted in accordance with Japan Medical Device GCP, ethical principles that have their origins in the Declaration of Helsinki, Pharmaceutical and Medical Device act, local regulations and this protocol. The study shall not begin until the required approval from the IRB and an acceptance of Chiken Todoke by regulatory authority have been obtained. Any additional requirements imposed by the IRB or regulatory authority shall be followed, if appropriate.

17.2. Investigator Responsibilities

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan, Japan Medical Device GCP, Pharmaceutical and Medical Device act, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB, and local laws and regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign or name and seal the Protocol Signature page or Protocol agreement documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Report to sponsor, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE.
- Report to the IRB and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by the national

regulations or this protocol or by the IRB, and supply BSC with any additional requested information related to the safety reporting of a particular event.

- Maintain the device accountability records and control of the device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

17.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

17.3. Institutional Review Board

Prior to gaining Approval-to-Enroll status, the investigational site will provide to the sponsor documentation verifying that their IRB is registered according to regulatory requirements.

A copy of the written IRB approval of the protocol and Informed Consent Form must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Annual IRB/EC approval and renewals will be obtained throughout the duration of the study as required by IRB requirements. Copies of the Investigator's reports and the IRB continuance of approval must be provided to the sponsor.

17.4. Sponsor Responsibilities

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC. Only authorized BSC personnel or a BSC representative including, but not limited to Contract Research Organization (CRO) will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

Boston Scientific will keep subjects' identifiable health information confidential in accordance with all applicable laws and regulations. Boston Scientific may use subjects' health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

The clinical trial organization including study sites is provided as an attachment to this protocol. BSC may utilize contract research organizations (CROs) or other contractors to act as their representative for carrying out designated tasks. Responsibilities for these entities are defined in the applicable contracts or agreements. Contact information for the CROs is provided as an attachment to this protocol.

The sponsor is responsible for providing the appropriate training about the study device implanting procedure to investigators.

These training may include the following;

- Overview of the study device
- Overview of the implant procedure
- Tips and size selection
- Hands-on training

- Proctoring

17.4.1. Role of Boston Scientific Representatives

Boston Scientific personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during implant, testing required by the protocol, and follow-ups. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC devices.

In addition, BSC personnel may perform certain activities to ensure study quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to protocol compliance.
- Reviewing collected data and study documentation for completeness and accuracy.

Boston Scientific personnel will not do the following:

- Practice medicine.
- Provide medical diagnosis or treatment to subjects.
- Discuss a subject's condition or treatment with a subject without the approval and presence of the HCP.
- Independently collect critical study data (defined as primary or secondary endpoint data).
- Enter data in electronic data capture systems or on paper case report forms.

17.5. Insurance

BSC will obtain proof and type of insurance coverage for subjects in the study.

18. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

19. Potential Risks and Benefits

19.1. *Anticipated Adverse Events and Risks Associated with the Study Device(s)*

The following anticipated adverse events (AE) have been identified for this study. Potential procedural risks associated with the BSJ003W implant procedure are similar to those encountered peri- and post-operatively for many routine catheterization procedures.

• Table 19-1: Anticipated Adverse Events

<ul style="list-style-type: none"> • Air embolism • Airway trauma • Allergic reaction to contrast media/medications or device materials • Altered mental status • Anemia requiring transfusion • Anesthesia risks • Angina • Anoxic encephalopathy • Arrhythmias • Atrial septal defect • AV fistula • Bruising, hematoma or seroma • Cardiac perforation • Chest pain/discomfort • Confusion post procedure • Congestive heart failure • Contrast related nephropathy • Cranial bleed • Death • Decreased hemoglobin • Deep vein thrombosis • Device embolism • Device fracture • Device thrombosis • Edema • Excessive bleeding • Fever • Groin pain • Groin puncture bleed • Hematuria • Hemoptysis 	<ul style="list-style-type: none"> • Hypotension • Hypoxia • Improper wound healing • Inability to reposition, recapture, or retrieve the device • Infection / pneumonia • Interatrial septum thrombus • Intratracheal bleeding • Major bleeding requiring transfusion • Misplacement of the device / improper seal of the appendage / movement of device from appendage wall • Myocardial erosion • Nausea • Oral bleeding • Pericardial effusion / tamponade • Pleural effusion • Prolonged bleeding from a laceration • Pseudoaneurysm • Pulmonary edema • Renal failure • Respiratory insufficiency / failure • Stroke – Ischemic • Stroke – Hemorrhagic • Surgical removal of the device • Systemic embolism • TEE complications (throat pain, bleeding, esophageal trauma) • Thrombocytopenia • Thrombosis • Transient ischemic attack (TIA) • Valvular damage • Vasovagal reactions
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19.2. *Risks associated with Participation in the Clinical Study*

Subjects who receive the BSJ003W Closure Device may stop warfarin therapy as early as the 45-day follow-up visit if they meet warfarin cessation guidelines; therefore, at that time, subjects may be at an increased risk of stroke. Warfarin and other oral anticoagulants are the most frequently utilized modality for reducing the risk of stroke in atrial fibrillation. The BSJ003W Closure Device is designed to be used instead of warfarin. The absence of an oral anticoagulant may represent a risk, especially if the device is not effective in preventing stroke.

19.3. *Possible Interactions with Concomitant Medical Treatments*

Refer to the warfarin, aspirin and thienopyridine package insert.

19.4. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

BSC will minimize risks of enrolled subjects by evaluating cause of the risks with experiences obtained from BSJ003W clinical studies and sales. Furthermore, minimization of the above mentioned risks should be tried through the following ways:

Target population of the study is those patients with high risk of stroke, and therefore, measures should be taken to prevent stroke by appropriately control the biggest risk factor of the stroke, blood pressure, in accordance with Japanese Guideline for the Management of Stroke (2015)²⁰. On the other hand, per Guidelines for management of anticoagulant and antiplatelet therapy in cardiovascular disease (JCS 2009)²¹, gastrointestinal bleeding from low dose Aspirin increases with age, and the target population of Aspirin treatment is older generation, and therefore, it is important to monitor gastrointestinal complications in order for Aspirin to be administered safely.

- Complete risk assessment of the study device before the study initiation per ISO14971
- Conduct safety test of BSJ003W using canine model to confirm safety and vascular compatibility
- Select investigators who understand risk, clinical indication and basic principal of percutaneous and trans-septal technique through the study device training.
- Clearly define inclusion and exclusion criteria so that only those patients who are eligible for the study to enroll.
- Align treatment and follow-up of subjects to the current medical practice.
- Safety evaluation process based on the threshold established in advance.

19.5. *Anticipated Benefits*

No direct subject benefit is expected from this study. Subjects enrolled in this study will receive the same clinical care as subjects who are routinely implanted with a BSJ003W Closure Device and not enrolled in this study. However, results from the data collected during this study may improve the management of BSJ003W subjects in the future; therefore, the subjects enrolled in this study may also benefit at a later stage.

The potential benefit of implanting the BSJ003W Closure Device is its expected ability to prevent thromboembolic events originating in the LAA. The BSJ003W Closure Device may protect against ischemic stroke and systemic thromboembolism. In subjects implanted with the device, the elimination of warfarin therapy may reduce bleeding complications, such as hemorrhagic stroke, associated with long-term anticoagulation. Economic and subject benefits related to the elimination of life-long compliance to warfarin therapy and the frequent blood tests and lifestyle changes associated with blood thinning medications are numerous.

19.6. *Risk to Benefit Rationale*

Risk management activities, including Hazard Analyses (HA) and Failure Mode Effects Analyses (FMEA), have been performed on the BSJ003W Closure Device to identify and analyze known and foreseeable hazards and reasonably foreseeable sequences or combinations of events that could result from using this product and the risks associated with each hazard. Mitigations have been implemented in the design, processes, and/or labeling and directions for use of the product to reduce the residual risk of each hazard as necessary and practicable. The HA has been reviewed and approved and the remaining risks are acceptable when weighed against the intended benefits to the subject.

In addition, investigational teams selected to conduct the study will be experienced and skilled in interventional cardiology and/or electrophysiology with transseptal and left heart experience, will have completed the BSJ003W Physician Training program and will have access to modern high technology medical facilities to conduct those procedures.

20. Safety Reporting

20.1. *Reportable Events by investigational site to Boston Scientific*

Any Adverse Event required by the protocol, experienced by the study subject after informed consent and once considered enrolled in the study (as defined in study subject classification section), whether during or subsequent to the procedure, must be recorded in the eCRF.

In accordance with requirements of the protocol (see Table 20.2-1 for AE definitions), it is the responsibility of the investigator to assess and report to BSC any event which occurs in any of following categories:

- All Serious Adverse Events
- All Investigational Device Deficiencies
- Unanticipated Serious Adverse Device Effects
- Unanticipated Adverse Device Effects
- New findings/updates in relation to already reported events
- All Device Related Adverse Events
- All Study Procedure Related Adverse Events
- Adverse Events related to BSJ003W (device thrombus, embolization, erosion, etc.)...
- All Bleeding Events regardless of relationship to the BSJ003W
- All Strokes (regardless of cause), Transient Ischemic (TIA) and Systemic Embolism regardless of relationship to the BSJ003W
- All serious adverse events, including: death of all cause (cardiovascular, non-cardiovascular, and unknown)

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

Underlying diseases are not reported as AEs unless there is an increase in severity of frequency during the course of the investigation.

Death should not be reported as an AE, but should only be reflected as an outcome of ONE(1) specific SAE (see table 20-2)

In-patient hospitalization is defined as the subject being admitted to the hospital, with the following exceptions.

- A hospitalization for a purpose of tests or a hospitalization that is uncomplicated and elective/planned (i.e., planned prior to enrollment) does not have to be reported as an SAE.
- If AEs occur during an elective/planned (i.e., planned prior to enrollment) hospitalization after enrollment, the complications and AEs must be reported as AEs or SAEs if they meet the protocol-specified definitions.

Refer to Section 18 for the known risks associated with the study device(s).

20.2. Definitions and Classification

Adverse event definitions are provided in Table 20.2 1. Administrative edits were made to combine the definitions from GCP, Order for Enforcement of the Pharmaceutical and Medical Device Affairs Law of serious adverse event from ISO 14155-2011 for clarification purposes.

Table 20.2-1: Adverse Event Definitions

Term	Definition
<p>Adverse Event (AE)</p> <p><i>Ref: GCP, Article 2 Part 20</i> <i>Ref: Order for Enforcement of the Pharmaceutical and Medical Device Law, Article 274</i> <i>Ref: ISO 14155:2011</i></p>	<p>Any untoward or unintended disease or injury or untoward clinical signs (including an abnormal laboratory finding) occurrence in subjects, users or other persons on whom the investigational medical device have been used whether or not related to the investigational device.</p> <p>NOTE 1: This definition includes events related to the investigational medical device.</p> <p>NOTE 2: This definition includes events related to the procedures involved.</p> <p>NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.</p>
<p>Adverse Device Effect (ADE)</p> <p><i>Ref: Order for Enforcement of the Pharmaceutical and Medical Device Law, Article 274</i> <i>Ref: ISO 14155:2011</i></p>	<p>Adverse event related to the use of an investigational medical device</p> <p>An event that is suspected of being caused by the use of an investigational medical device or a communicable disease suspected of being caused by its use.</p> <p>NOTE 1: This definition includes any adverse events resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation or operation, or any malfunction of the investigational medical device.</p> <p>NOTE 2: This definition includes any event resulting from use error or intentional abnormal use of the investigational medical device.</p> <p>Note3: The definition of “an event that is suspected of being caused by the use of an investigational medical device” refers to event is other than that whose cause and effect relationship with the investigational medical device can be denied, and includes that whose cause and e effect relationship is uncertain.</p> <p>Note 4: The definition of “a communicable disease that is suspected of being caused by its use” refers to the suspected contamination of the investigational medical device with biological ingredients by pathogen.</p>
<p>Serious Adverse Event (SAE)</p> <p><i>Ref: ISO 14155:2011</i></p>	<p>Adverse event that:</p> <ul style="list-style-type: none"> • Led to death, • Led to serious deterioration in the health of the subject, as defined by either <ul style="list-style-type: none"> ○ a life-threatening illness or injury, or ○ a permanent impairment of a body structure or a body function, or ○ in-patient hospitalization or prolonged hospitalization , or ○ medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death, or a congenital abnormality or birth defect. <p>NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the Clinical Investigation Plan, without serious deterioration in health, is not considered a serious adverse event.</p>
<p>Serious Adverse Device Effect (SADE)</p>	<p>Adverse device effect that resulted in any of the consequences characteristic of a serious adverse event.</p> <p>Serious adverse effect that is suspected of being caused by the use of an</p>

Table 20.2-1: Adverse Event Definitions

Term	Definition
<i>Ref: Order for Enforcement of the Pharmaceutical and Medical Device Law, Article 274</i> <i>Ref: ISO 14155:2011</i>	investigational medical device or serious communicable disease suspected of being caused by its use.
Unanticipated Adverse Device Effect (UADE) <i>Ref: 21 CFR Part 812</i>	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) <i>Ref: GCP, Article 28 Part 2 and 3</i> <i>Ref: ISO 14155:2011</i>	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. NOTE 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency <i>Order for Enforcement of the Pharmaceutical and Medical Device Law, Article 274)</i> <i>Ref: ISO 14155:2011</i>	An inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

20.3. Relationship to Study Device(s)

The Investigator must assess the relationship of the AE to the study device or procedure. See criteria in Table 20.3-1:

Table 20.3-1: Criteria for Assessing Relationship of Study Device or Procedure to AE

Classification	Description
Not Related	<p>Relationship to the device or procedures can be excluded when:</p> <ul style="list-style-type: none"> - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the investigational device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Unlikely Related	<p>The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.</p>
Possibly Related	<p>The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.</p>
Probably Related	<p>The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.</p>
Causal Relationship	<p>The serious event is associated with the investigational device or with procedures beyond reasonable doubt when:</p> <ul style="list-style-type: none"> - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that <ul style="list-style-type: none"> o the investigational device or procedures are applied to; o the investigational device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

20.4. Investigator Reporting Requirements

The communication requirements for reporting to BSC are as shown in Table 20.4-1.

Note: The “become aware date” for an event that requires reporting per the protocol is the date that investigator or trained study staff are notified of the event.

Table 20.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline pre-market studies*
Unanticipated Adverse device Effect(UADE)/Unanticipated Serious Adverse Device Effect (USADE)	Complete AE eCRF page with all available new and updated information.	<ul style="list-style-type: none"> • Within 1 business day of first becoming aware of the event. • Terminating at the end of the study
Serious Adverse Event (SAE)	Complete AE eCRF page with all available new and updated information.	<ul style="list-style-type: none"> • Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (unidentified) for reported event upon request of the sponsor	<ul style="list-style-type: none"> • At request of sponsor
Serious Adverse Device Effects (SADE)	Complete AE eCRF page with all available new and updated information.	<ul style="list-style-type: none"> • Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (unidentified) for reported event	<ul style="list-style-type: none"> • When documentation is available
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete CRF fields/pages with all available new and updated information. Provide all relevant source documentation (unidentified) for reported event upon request of the sponsor	<ul style="list-style-type: none"> • Within 3 calendar days of first becoming aware of the event. • Reporting required through the end of the study
Adverse Event (AE) including Adverse Device Effects (ADE)	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	<ul style="list-style-type: none"> • In a timely manner (e.g. Recommend within 10 business days) after becoming aware of the information • Reporting required through the end of the study

Abbreviations: AE=adverse event; CRF=case report form; IDE=Investigational Device Exemption; * Please note that pre-market studies are clinical studies with investigational devices or with medical devices that bear the regulatory approval and are not being used for the same approved indications.

20.5. Boston Scientific Device Deficiencies

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the investigational device(s) will be provided. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not adverse events. However, an adverse event that results from a device failure or malfunction, would be recorded as an adverse event on the appropriate eCRF.

Any Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.

20.6. Reporting to Regulatory Authorities / IRBs / Investigators

BSC is responsible for reporting adverse event information to all participating Principal Investigators and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the IRB and regulatory authorities of UADE and SAE as required by local/regional regulations.

20.7. CEC (Clinical Events Committee) Adjudication Events

As an Independent CEC will be adjudicating events for this study, appropriate medical records from investigative sites must be sent to Boston Scientific.

Events which require source documents include:

- Stroke (all causes)
- TIA
- All deaths throughout the study
- Systemic embolism
- Major open cardiac and/or endovascular surgery through 7 days or hospital discharge (whichever is later)
- Major bleeding defined by BARC 3 or 5
- Clinically overt non-fatal bleeding defined by BARC 2
- Other events, at the discretion of Boston Scientific

20.7.1. Stroke Reporting Documentation Recommendations

In the event that a subject experiences a stroke or SE during the course of the study, supporting documentation will be requested by the sponsor. This information may include neurologist consultation note(s), MRI/CT imaging, radiology reports, additional NIHSS/MRS/Barthel Index evaluations, or statement from the investigator. In addition, a search for alternative causes of stroke (including hypercoagulable work-up) and TEE evaluation at the time of any stroke or embolic event is strongly encouraged to help better ascertain the mechanism of all strokes. An optimal TEE evaluation includes, where feasible based on subject status and technical considerations, evaluation of:

- LA thrombus – size, location, mobility, etc.
- BSI003W Device Seal or presence (and measurement) of peri-device flow
- BSI003W Device thrombus or pannus – size, location, mobility, etc.
- Agitated saline contrast injection to evaluate presence of residual right to left shunt at the atrial level (persistence of PFO or residual puncture hole from transseptal catheterization for device placement)
- Presence and grade of ascending and arch aortic atheroma
- Presence of worsening left ventricular dysfunction, “new” regional wall motion abnormality or presence of LV thrombus (LVEF data may be supplemented/substituted by TTE where appropriate, in addition to TEE parameters above)

20.7.2. All Bleeding Events Reporting Documentation Recommendations

In the event that a subject experiences all bleeding events during the course of the study, supporting documentation including a statement from the investigator will be requested by the sponsor.

20.8. *Device Thrombus*

The most accurate determination of whether thrombus has formed on the surface of the BSI003W Device is through TEE evaluation. In the case of thrombus on the atrial facing side of the device, anticoagulation therapy should be initiated for approximately 12 weeks, or a longer period of time per hospital standard of care, for treatment of thrombus. After the course of anticoagulation therapy, a repeat TEE evaluation should be performed to confirm the thrombus has resolved. Cessation of anticoagulation after this time point is at the discretion of the investigator.

20.9. Death Reporting

- A subject death that occurs during the study should be reported to Boston Scientific as soon as possible and, in any event, within 3 calendar days of center notification. The center's IRB must be notified of any deaths in accordance with that center's IRB policies and procedures.

Source documentation of death will include a detailed narrative (death letter) that provides detailed information describing the circumstances surrounding the death and is signed by the principal Investigator or authorized co-Investigator. For any information which may be unknown, the investigator must still address the relevant area in the detailed death narrative. A death narrative in the local language is acceptable. The death narrative must include all of the following, if available:

- Date and time of death
- Place death occurred
- Immediate cause of death
- Whether the death was related to the investigational device or clinical investigation, procedure, or patient condition
- Whether or not the death was witnessed
- Whether the subject had any Transient Ischemic Attack/Stroke/Bleeding prior to the death
- Any other circumstances surrounding the death
- Approximate time interval from the initiating event to death (temporal course)
- Investigator or co-Investigator signature and date

Any information listed above that is unavailable or unknown must be specified as unavailable or unknown, as applicable, in the narrative. Also submit the following documentation:

- A copy of the relevant medical records from enrollment to death, this will include H & P, consults, test results, operative reports, and/or progress notes from the hospital chart and clinic chart
- Death certificate (if available)
- Autopsy report (if applicable)

21. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, Japan Medical Device GCP, Pharmaceutical and

Medical Device act, and Regulatory authority body. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the site's IRB or central IRB, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's IRB. Any modification requires acceptance from BSC prior to use of the form. The ICF must be in a language understandable to the subject. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form. Signatures can be replaced by printed name and seal of appropriate individuals.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements. Any violations of the informed consent process must be reported as deviations to the sponsor, the site and/or its IRB, as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB. The new version of the ICF must be approved by the IRB. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB. The IRB will determine the subject population to be re-consented.

22. Committees

22.1. Safety Monitoring Process

To promote early detection of safety issues, Boston Scientific reviews adverse events and device deficiencies per the Safety Plan. Events are reviewed with BSC Safety Office and success of this program requires dynamic collection of unmonitored data as soon as the event is reported. This is expedited through BSC's Global Safety Office, which is responsible for coordinating the collection of information for the subject dossier from the centers and core laboratories. During regularly scheduled monitoring visits, clinical research monitors will support the dynamic reporting process through their review of source document information.

22.2. Clinical Event Committee

A Clinical Events Committee (CEC) is an independent group of individuals with pertinent expertise that reviews and adjudicates important events for inclusion into the primary and secondary endpoints. The events that the CEC will review for this study are the primary and secondary endpoint events and include: all stroke, TIA, all-cause death, systemic embolism, device and/or procedure-related events which resulted in open cardiac/endovascular surgery and all bleeding events including major bleeding. Any additional event which the BSC Safety Office feels requires the review of an independent committee may also be sent. The CEC will review a safety event dossier, which may include copies of subject source documents provided by study centers and confirm inclusion of the event into the primary and secondary endpoints. CEC responsibilities, qualifications, membership, and committee procedures are outlined in the CEC charter. Name and address of CEC are included in the attachment of this protocol.

23. Suspension or Termination

23.1 Premature Termination of the Study

Boston Scientific Corporation reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, the sites and regulatory authorities will be notified in writing in the event of study termination.

23.1.1 Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following.

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development of the device.

23.2 Termination of Study Participation by the Investigator or Withdrawal of IRB Approval

Any investigator or IRB in the WATCHMAN Japan Study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated IRBs and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

23.3 Requirements for Documentation and Subject Follow-up

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating sites by Boston Scientific. The IRB and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB terminates participation in the study, participating investigators, associated IRBs and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The Principal Investigator or his/her designee must return all study-related documents and investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

23.4 Criteria for Suspending/Terminating a Study Site

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of site participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the site will continue to be followed per the investigator's standard of care for subjects. The Principal Investigator at the site must make provision for these follow-up visits unless BSC notifies the investigational site otherwise.

24. Publication Policy

BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific Corporation adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors

(ICMJE; <http://www.icmje.org>). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

25. Bibliography

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26. Abbreviations and Definitions

26.1. Abbreviations

Abbreviations are shown in Table 26.1-1.

Table 26.1-1: Abbreviations

Abbreviation/Acronym	Term
ADE	Adverse device effect
AE	Adverse event
AF	atrial fibrillation
ASA	acetylsalicylic acid
ASD	atrial septal defect
BI	Barthel Index
CEC	clinical event committee
CHADS ₂	scoring system used to identify subjects in need of anticoagulation (congestive heart failure, hypertension, age \geq 75years, diabetes, previous stroke [doubled])
CHA ₂ DS ₂ -VASc	complemental scoring system used to identify subjects in need of anticoagulation (congestive heart failure, hypertension, age \geq 75y [doubled], diabetes, previous stroke [doubled], vascular disease, age65-74y, sex category)
CHF	Congestive heart failure
CRF	Case report form
DAPT	Double Antiplatelet Therapy
DOAC	Direct oral anticoagulant
EU	European Union
FDA	Food and Drug Administration
eGFR	(estimated) glomerular filtration rate
ICF	Informed consent form
INR	international normalized ratio
IRB	Institutional Review board
ITT	intention-to-treat
LAA	left atrial appendage
LVEF	left ventricular ejection fraction
MRS	Modified Rankin Scale
MV	Mitral valve
NIHSS	NIH stroke score
NVAF	non-valvular atrial fibrillation
PFO	patent foramen ovale
PG	performance goal
PMA	premarket approval
SADE	Serious adverse device effect
SAE	Serious adverse event
TEE	transesophageal echocardiogram
TIA	transient ischemic attacks
TTE	transthoracic echocardiogram

Table 26.1-1: Abbreviations

Abbreviation/Acronym	Term
ADE	Adverse device effect
AE	Adverse event
UADE	Unanticipated adverse device effect
USADE	Unanticipated serious adverse device effect

26.2. Definitions

26.2.1. Stroke/TIA definitions

Broad definitions:

Neurological deficit: An acute episode of a focal or global neurological deficit with at least one of the following:

- Change in the level of consciousness
- Hemiplegia
- Hemiparesis
- One-sided numbness or sensory loss
- Dysphasia or aphasia
- Hemianopia
- Amaurosis fugax
- Any other neurological signs or symptoms consistent with stroke

In addition, there are no other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacologic influences), to be determined by or in conjunction with the designated neurologist.

Stroke: Stroke is defined by either one of the following:

- Duration of focal or global neurological deficit >24 h.
- Duration of focal or global neurological deficit <24 h in case of imaging-documented new hemorrhage or infarct.
- A neurological deficit resulting in death;

Transient ischemic attack: A TIA is defined by any neurological deficit not satisfying the above criteria for stroke, specifically a deficit lasting <24 h without imaging-documented new hemorrhage or infarct. .

Stroke diagnostic criteria:

- Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, haemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke;
- Duration of a focal or global neurological deficit ≥ 24 h; OR, 24 h, if therapeutic intervention(s) were performed (e.g. thrombolytic therapy or intracranial

- angioplasty); OR available neuroimaging documents a new haemorrhage or infarct;
OR the neurological deficit results in death
- No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycaemia, peripheral lesion, pharmacological influences)
 - Confirmation of the diagnosis by at least one of the following:
 - Neurology or neurosurgical specialist
 - Neuroimaging procedure (MR or CT scan or cerebral angiography)
 - Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial haemorrhage)

Stroke Types:

Ischemic: An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction

Hemorrhagic:

- intracerebral: rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.
- subarachnoid: rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma.

Silent infarction: Imaging or neuropathological evidence of CNS infarction, without a history of acute neurological dysfunction attributable to the lesion.

Stroke caused by cerebral venous thrombosis: Infarction or hemorrhage in the brain, spinal cord, or retina because of thrombosis of a cerebral venous structure. Symptoms or signs caused by reversible edema without infarction or hemorrhage do not qualify as stroke.

Not otherwise specified: an episode of acute neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting ≥ 24 hours or until death, but without sufficient evidence to be classified as one of the above

(from Kappetein, A.P., et al., J Am Coll Cardiol, 2012. 60(15): p. 1438-54)

26.2.2. Classification of Bleeding events

In response to the need to develop, disseminate, and ultimately adopt standardized bleeding end-point definitions for subjects receiving antithrombotic therapy, the Bleeding Academic Research Consortium (BARC) convened in February 2010 at the US Food and Drug Administration (FDA) headquarters in White Oak, MD. BARC effort brought together representatives from academic research organizations, the FDA, the National Institutes of Health, and pharmaceutical and cardiovascular device manufacturers and independent physician thought leaders in the field of cardiovascular disease to develop consensus bleeding definitions that would be useful for cardiovascular clinical trials. Application of these definitions is recommended for both clinical trials and registries:

Type 0:

No bleeding

Type 1:

Bleeding that is not actionable and does not cause the subject to seek unscheduled performance of studies, hospitalization, or treatment by a health-care professional; may include episodes leading to self-discontinuation of medical therapy by the subject without consulting a health-care professional.

Type 2:

Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria:

- requiring nonsurgical, medical intervention by a health-care professional,

- leading to hospitalization or increased level of care, or
- prompting evaluation

Type 3:

Type 3a:

- Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL* (provided hemoglobin drop is related to bleed)
- Any transfusion with overt bleeding

Type 3b:

- Overt bleeding plus hemoglobin drop ≥ 5 g/dL* (provided hemoglobin drop is related to bleed),
- Cardiac tamponade,
- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid),
- Bleeding requiring intravenous vasoactive agents

Type 3c:

- Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal),
- Subcategories confirmed by autopsy or imaging or lumbar puncture,
- Intraocular bleed compromising vision.

Type 4:

- CABG-related bleeding,
- Perioperative intracranial bleeding within 48 h,
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-h period,
- Chest tube output more than or equal to 2L within a 24-h period

Type 5:

Fatal bleeding

Type 5a:

Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b:

Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

(from *Circulation*. 2011; **123**(23): 2736-47)

27. Appendices

27.1. Clinical Trial Organization

In the following cases, special sentences must be described in the protocol according to Japan GCP and GCP manual (article 7 of Japan Medical Device GCP).

- Investigational device affords no intended clinical benefit to the subjects
- Informed consent is expected to be difficult to obtain from subject
- Life-saving clinical trial in an emergency situation, when the clinical trial is planned to be conducted even when the preliminary consent of the prospective subject cannot be

obtained and the legally acceptable representative of the prospective subject cannot be reached for informed consent